"In situ" Corneal and Contact Lens Thickness Changes with High Resolution OCT

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Running head: Cornea and Contact Lens Thickness Changes with HR OCT

ABSTRACT

Purpose: To show the utility of high resolution spectral domain optical coherence tomography (HR SOCT) for the *in situ* evaluation of epithelial, stromal and contact lens (CL) thickness changes under closed-eye conditions without lens removal.

Settings: Clinical and Experimental Optometry Research Lab, University of Minho, Portugal.

Methods: Eight young healthy patients wore a thick soft CL during 90 minutes under closed-eye conditions and measures of epithelial and stromal corneal thickness were obtained at regular intervals using a HR SOCT (Copernicus HR, Optopol Tech. SA, Poland).

Results: Minimal changes in epithelial thickness were detected with a transient statistically significant increase in epithelial thickness in the fellow control eye 30 minutes after insertion ($p=0.028$). A significant and progressive increase in stromal thickness up to 8% after 90 minutes of lens wear was observed at a constant rate of 2.5% every 30 minutes, being statistically significant in all observations ($p<0.001$). Fellow control eye also showed a significant increase in stromal thickness at a much lower rate of 0.5% every 30 minutes. Lens thickness decreased significantly by 2% after 90 minutes of lens wear under closed eye conditions ($p<0.001$). Individual analysis showed that all eyes displayed stromal swelling, while only half of them showed epithelial swelling.

Conclusion: Increase in stromal thickness and a slight decrease in lens thickness were observed in response to a hypoxic stimulus under closed eye conditions. High resolution spectral domain HR SOCT is a powerful tool to investigate *in vivo* the physiological interactions between cornea and contact lenses.

INTRODUCTION

Ophthalmic imaging techniques have evolved tremendously for the past ten years. Optical tomographs[1], high-resolution ultrasound biomicroscopy (UBM)[2] and confocal microscopy[3] had been at the forefront of this evolution. However, accurate quantification and three dimensional reconstruction of different corneal layers could not be easily determined in clinical practice until the development of optical coherence tomography (OCT) technology.

One of the fields taking advantage from all these advances has been the study of corneal physiology in response to contact lens (CL) wear. For several years the evaluation and imaging of the effects of CL on corneal structure has been accomplished using clinically available instrumentation such as optical pachometers attached to the slit-lamp, specular microscopes and more recently confocal microscopes., Those techniques, however, 1) do not provide cross-sectional imaging of the cornea with as much resolution as a slit lamp to accurately differentiate between different layers, 2) were limited to imaging only one layer at a time, as with specular microscopy, 3) have limited potential to be implemented in regular clinical practice, as occurs with UBM, or 4) have limitations in building up a three-dimensional reconstruction of the corneal structure. Only some customized instruments allowed the measurement of epithelial thickness[4], which is of major interest now in corneal reshaping through CL[5].

Currently, the evaluation of the corneal thickness profile layer by layer and the evaluation of the relationship between cornea and contact lenses can be assessed *in vivo* using OCT technology [6-9]. Some studies have also obtained reliable results of total corneal thickness without lens removal, which is more convenient for the patient and reflects a more realistic evaluation of the corneal response while using a CL.[10] Furthermore, this may be mandatory when therapeutic contact lenses are in place to avoid any traumatic interaction with the ocular surface during repeated insertion and removal of the lens.

Several reports using laboratory prototypes have shown promising results with regards to the sensitivity of high resolution OCT technology for the assessment of the lens to cornea relationships.[11-13] The authors of the present study have recently shown that such features might also be depicted from commercially available high resolution OCT devices[14]. However no study has yet explored these capabilities, or has shown applications in the field of the evaluation of corneal response to metabolic stress in the stroma and epithelial layers separately using current commercially available high resolution OCT technology.

Considering the evaluation of corneal response to CL without removing the lens, and with the advent of commercially available devices based on high resolution OCT technology, the present study aims to assess the feasibility of measuring epithelial and stromal corneal thickness separately as well as CL thickness *in situ*. Furthermore, the evaluation of the potential impact of the hypoxic stimulus on the epithelium and stromal thickness induced by a thick soft CL under closed eye conditions was also carried out.

METHODS

Subjects

Eight young healthy subjects aged 21 to 25 years of age (23.34±1.43) were randomly fitted on their right or left eye with a thick soft CL (described below) while the fellow eye remained as a control without a CL. Lenses were worn for 90 minutes with both eyes closed. Inclusion criteria required that subjects were not taking any ocular or systemic medication, had not worn contact lenses prior to the study and had no ocular or systemic disease. The study was approved by the Institutional Review Board (University of Minho, Braga, Portugal) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before all the interventions and they also gave their consent to treat their clinical data anonymously for research purposes.

Instrumentation

The instrument used was a spectral domain high resolution optical coherence tomographer (Copernicus HR SOCT, Optopol Technology SA, Zawiercie, Poland). This device was conceived as a posterior segment high resolution OCT providing axial resolutions of 3 micron using an 840nm wavelength, but it can be also used for anterior segment viewing through a coupling device, also commercially available. For anterior segment imaging the manufacturer claims an axial resolution of 2.88 microns. Unless stated otherwise, a 5 mm observation field was obtained for all the images. Below in this section the method devised to improve the accuracy and reliability of the measurements taken is presented.

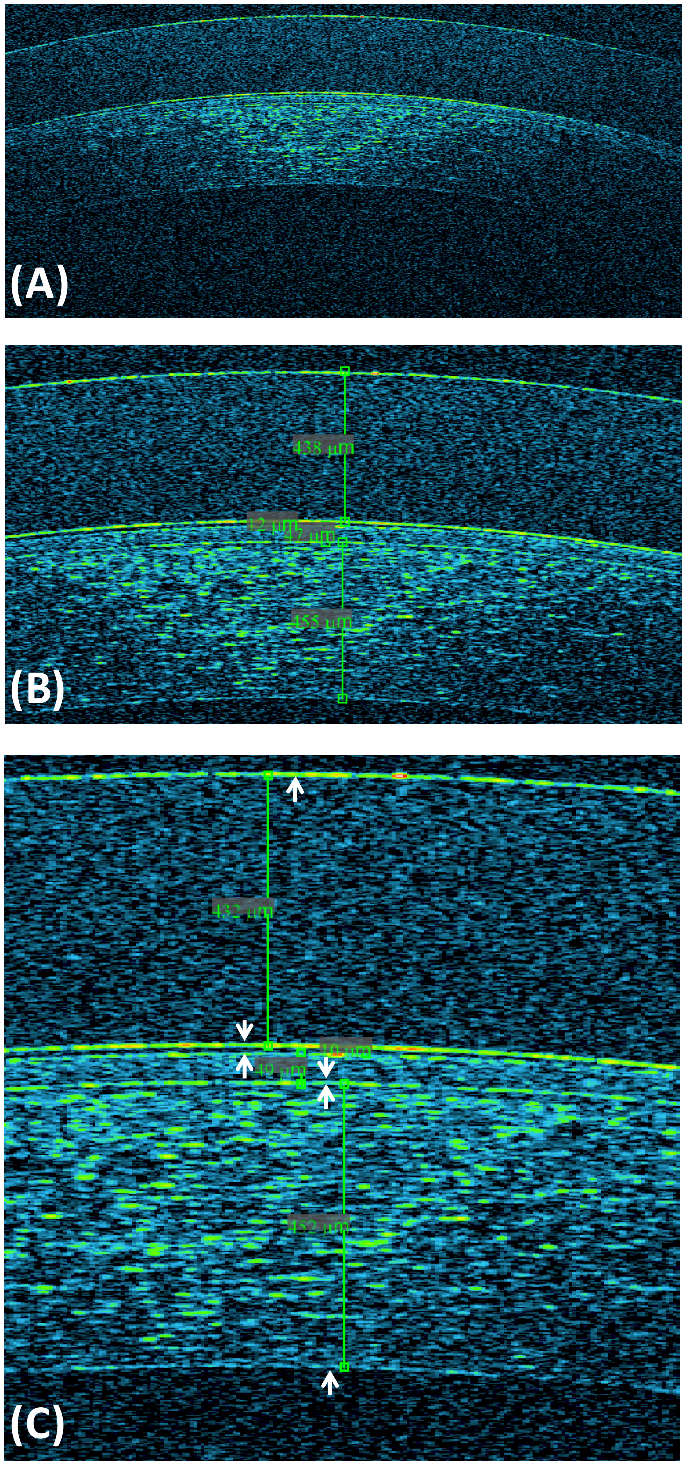

Figure 1. Image of an OCT section of the cornea highlighting the limits of the layers to be measured (tear-epithelium, epithelium-Bowman, Bowman-stroma, stroma-aqueous) at different magnification to highlight the limits and improve detection reliability. Arrows hightlight reference limits for measurements.

Contact Lenses

The Soft K® soft CL (Soflex Isralens Ltd., Misgav, Israel) is made of a non-ionic high-water content material (58%) under the generic name GM3 which is a copolymer of glycerol-metacrilate (GMMA) and vinyl-pyrrolidone (VP). As described by the manufacturer, this design is available in two different materials. Eni-Eye Soft K® and Eni-Eye Soft K® Toric made of a copolymer of N-vinyl pyrrolidone (NVP), methyl methacrylate and cyclohexyl methacrylate 2-ethoxyethyl methacrylate cross-linked with allyl methacrylate (33% xylofilcon A, 67% water @ 20º); and Soflex Soft K® Toric made of a copolymer of glycerol methacrylate and vinyl pirrolidone (42% acofilcon A, 58% water @ 20º). Technical parameters of the lens are presented in *table 1*.

The lenses were fitted on a second appointment to find the best lens-to-cornea relationship under slit-lamp evaluation. The aim was to obtain good centration in order to warrant that all patients had the same part of the lens over the central cornea to be evaluated and that the lens was not either too tight to create lens vaulting and excessive corneal clearance or too flat that would compress the central cornea, these effects could be significant for a lens of this thickness. Although we cannot remove the mechanical interaction that could potentially affect the lens-to-cornea relationship the presence of a tear film layer between the lens and the cornea as shown in *figure 1* will keep this potential contribution to the minimum possible. All patients were evaluated between 14:00 and 17:00 to minimize diurnal variations in thickness or to avoid potential variations in hydration control during the day.

Table 1. Technical details of the lenses used

Brand	**Soft K**
Manufacturer	Soflex
Material (USAN)	Filcon2 II (copolymer of NVP and MMA)
Dk (barrer)	30
Water Content (%)	67.5
t_c (mm)	0.36 (-3.00)
Power (D)	-6.00
Overall Diameter (mm)	14.2
Base Curve Radius (mm)	7.3 / 7.6 / 7.9

D= Diopters
Barrer = 10^{-11} (cm^2/sec)[ml O_2/(ml x mmHg)]
t_c= central thickness.

Fitting and Measuring Protocol

All patients were scheduled for an office visit in order to fit the lenses they would wear on the day of study. By trying different base curve radii, it was ensured that neither too flat nor too steep lenses were fitted to minimize mechanical effects to the corneal epithelium confounding the potential outcomes of the study, i.e. the evaluation of the physiological response of the cornea to CLwear. After two weeks all subjects were again scheduled to wear their lenses under closed eye conditions in one eye only randomly assigned. The fellow eye, without a CL, acted as a control. It was ensured that all patients had woken-up at least 4 hours before attending the laboratory on that day. Additionally, all measurements were done between 14:00 and 17:00 in order to minimize potential diurnal variations in corneal hydration control[9;15;16].Measurements were taken at baseline before lens insertion and immediately after insertion of the lens on one eye (t=0'). Thereafter, every 30 minutes (t=30', t=60' and t=90') during period of bilateral eye closure, the patient was guided to the examination room with both eyes still closed and placed at the OCT chin-rest for measurements. Because the situation had not changed in the control eye between baseline and after insertion (t=0') of the lens in the fellow eye, no measure of corneal thickness was obtained at t=0 in the control eye, assuming the same thickness values obtained in baseline measures. Once all alignments were obtained the patient was asked to open the eyes and with minimal additional adjustments both eyes were imaged within 20 seconds. To ensure that measurements are reliably obtained at the same corneal location, the specular reflex induced when the incident beam is perpendicular to the corneal apex was used as a reference; at this moment, minimal changes on instrument location was done to get an image free from specular reflex noise. Using this approach we have been able to measure contact lens, epithelial and stromal thickness from 3 repeated images of the same eye with a standard deviation of 3.46, 1.15 and 2.31 µm, respectively. These values represent approximately 0.8%, 2.56%, and 0.47% of the average thickness measured, respectively (*unpublished data*).

In order to improve the resolution of the measuring technique, the image was magnified to its maximum using the software of the instrument as seen in *figure 1* and measurements were obtained always along the central location of the visualization screen. *Figure 1C* depicts the criteria to visually detect the limits for measuring each one of the different layers. All measures were done by an experienced observer using the same criteria. One challenging aspect of edge detection to measure CL and epithelial thickness are the temporal changes experienced by the post-lens tear film as the posterior lens surface and anterior epithelial surface might be confounded when they get closer to each other as the lens settles. However, the criteria used to detect edges and graphically illustrated in *figure 1* allows as to avoid the potential adverse influence of temporal changes on the post-lens tear film on estimations of the epithelial and CL thickness. Three images were obtained from each patient at each measuring time and averaged considering that this methodology has shown good repeatability in preliminary assessments carried at our lab with the instrument. A trained technician masked to the time when the images where taken obtained all the measurements according to the protocol mentioned above.

Statistical Analysis

Normality of data distribution for different variables either as absolute values or percentages was assessed by a Kolmogorov–Smirnov normality test. The time course of changes in stromal and epithelial thickness was plotted against time and statistically compared to baseline using Wilcoxon signed ranks test eyes wearing contact lenses and controls, separately. Comparison between controls and CL wearing eyes were performed at each examination time using Mann-Whitney test. The level of statistical significance was set at $\alpha=0.05$.

RESULTS

Figure 2 shows the epithelial thickness changes in the eye wearing the lens and in the fellow control eye as percentage of the baseline thickness. The changes in epithelial thickness are subtle but deserve mentioning. Although very small, epithelial thickness changes are in the order of 2-4% when analyzed as percentages compared to baseline. These changes are not statistically significant, except for the control eyes at t=30 (p=0.018 for values in microns and p=0.028 for values as percentages). There is a trend towards an increase in the fitted eye, while the control eye shows a initially higher trend towards an increase for the first 30 minutes, followed by a rapid return to baseline after 30 minutes of lens wear.

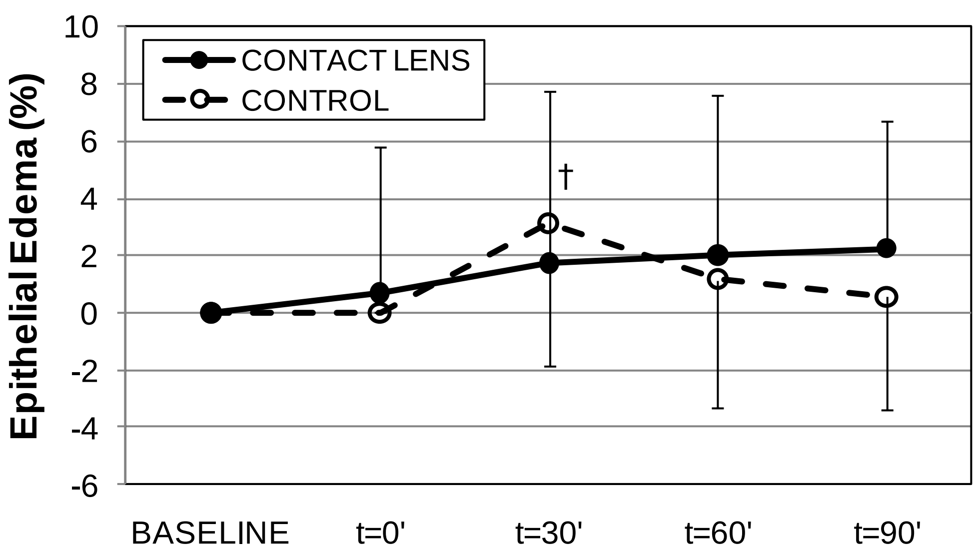

Figure 2. Changes in epithelial thickness for eyes wearing contact lenses under closed eye conditions and control eyes at baseline, immediately after lens insertion (t=0’) and after 30 (t=30’), 60 (t=60’) and 90 minutes (t=90’). Error bars represent standard deviation. In control eyes, t=0’measures are the same obtained at baseline.

Four of the subjects either did not display changes or baseline data was slightly higher, while in the remaining four cases, there was a remarkable increase of thickness.. In four cases there was an increase of thickness, in three cases there was not any noticeable change and in one case there was a slight thinning effect over time.

Figure 3 shows the stromal thickness changes in the eye wearing the lens and in the fellow control eye as percentage of the baseline thickness. A significant increase in stromal thickness is observed immediately after lens insertion in the fitted eye and a continuous increase of 2.5% per each 30 minutes is observed thereafter until the 90 minutes (final measurement). In the control eyes there was also a significant increase in stromal thickness at 30’ and thereafter, although in this case the greater increase is observed during the first 30 minutes (about 2%) with minor changes afterwards.

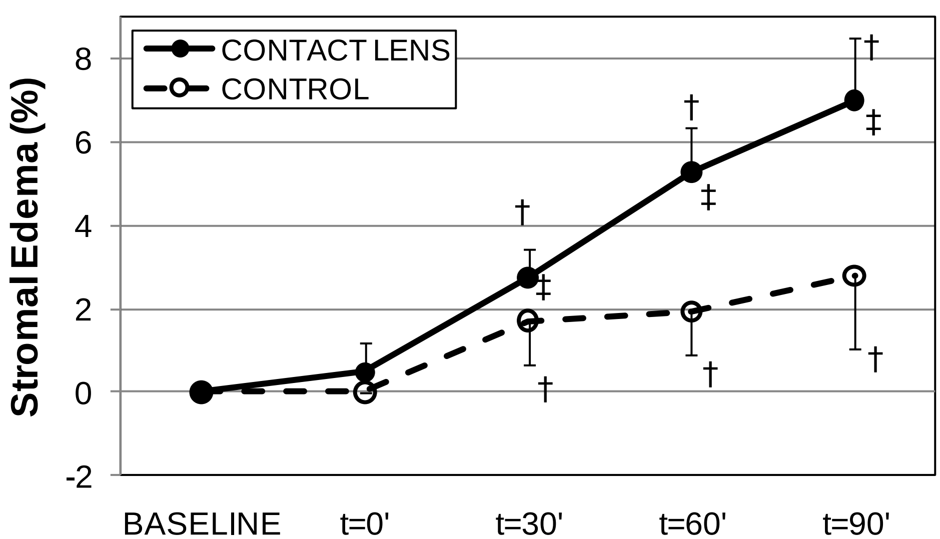

Figure 3. Changes in stromal thickness for eyes wearing contact lenses under closed eye conditions and control eyes at baseline, immediately after lens insertion (t=0’) and after 30 (t=30’), 60 (t=60’) and 90 minutes (t=90’). Error bars represent standard deviation. In control eyes, t=0’measures are the same obtained at baseline.

All fitted eyes swelled by 20 to 40 microns (average: 7.00±1.50%, range: 4.4 to 8.9%). In the control eye, all corneas but one swelled slightly by 5 to 20 microns (average: 2.60±1.76%, range: 1.70 to 5.10%)

There was a positive and significant correlation between stromal edema in fitted and control eyes after 90 minutes (Spearman Rho=0.530; p=0.035), with weaker and non-significant correlations for shorter times of CL wear (60’ and 30’).

No differences were observed in stroma and epithelial thickness measures between baseline and immediately after lens insertion with average differences below 3 and 0.5 microns, respectively (p>0.05).

There was a small but statistically significant change in lens thickness during the period of lens wear.

DISCUSSION

The present study has shown the potential of HR SOCT for the *in vivo* assessment of corneal response to CL wear without lens removal as well as the response of the lens material to ocular surface environment under closed eye conditions. Previous studies have shown the potential of this technology for the evaluation of the lens-to-cornea relationships, but the present study expands this role bringing forward interesting opportunities for ocular surface research[12;13].

In the present study, the average 7% increase in stromal thickness for eyes wearing the lenses and 2.5% for control eyes match well the results of Fonn et al for low-Dk lenses after 8 hours of lens wear[17]. The fact that those values were achieved just 1.5 hours after CL insertion is due to the low transmissibility values induced by the thick design of the lens, rendering Dk/t values well below 10 barrer/cm. This Dk/t would imply equivalent oxygen percentage (EOP) values below 2% and biological oxygen apparent transmissibility (BOAT) below 10%[18],

With regards to epithelial thickness, previous studies have shown non- significant change in epithelial thickness in response to hypoxic stimulus[8]. Long term results have shown that a significant decrease in epithelial thickness[19] seems to reverse after lens wear cessation[4]. In the present study, epithelial thickness showed a non-significant increase in half of the subjects enrolled. Although epithelial edema in response to hypoxic stimulus might not be present in all subjects, HR SOCT could provide with a more accurate insight into this response. For example, an increase in epithelial back-scatter was observed by Wang et al. analyzing OCT sectional images[7], what could be related to changes in the physical properties of this layer, and an increase in thickness must not be therefore discarded given the preliminary data shown in the present report. The transient epithelial increase observed here might reflect an epithelial edema related to physiological changes in the tear film immediately after CL insertion. Any increase in reflex tear secretion will induce a drop in tear osmolarity, hence favoring a potential epithelial swelling. This response was not observed in all subjects examined, however.

In a separate study, Wang et al found a transient non-significant increase in epithelial thickness after removal of an hypoxic stimulus covering the cornea for 3 hours[6]. This somewhat surprising observation certainly deserves further attention in future studies designed to investigate the potential influence of mechanical interaction between such thick lenses or even rigid lenses and the epithelial physiological response. Meanwhile it may be argued that any increase in epithelial thickness must be considered as an acute response, since in the long term epithelial thinning seems to be the common consequence to long-term hypoxia in eyes wearing low-Dk CL[4;19]. As per the authors' experience, researchers and clinicians should be cautious when assessing the boundaries of the epithelial layer since the post-lens tear film could challenge the ability to precisely determine this limit,, thus becoming a potential source of error. In the present study the magnification tool provided by the original software was used to exactly determine the pixel on screen that limits the anterior epithelial layer. Criteria used to detect the anterior epithelial limit and posterior lens limit avoid the potential confusion between these layers and the post-lens tear film when the lens settles down over time, as explained in methods section. Further improvements in detection software would be necessary to improve objectivity in these measures and allow obtaining accurate values of thinner layers (i.e. epithelium, post-lens and pre-lens tear film…) with no intervention from the observer.

One limitation of the present study is the limited sample size. However, given the small variability of repeated measures with the present OCT technology, even under these circumstances, the statistical power guaranteed the potential for detection of thickness changes higher than 2.5, 1.5 and 2.4 µm for CL, epithelium and stroma, respectively. Smaller changes might not be detected with this sample but they could be also considered as clinically meaningless. Another limitation is that the recovery of the corneal layers from the hypoxic stress induced was not studied, however this effect has been documented in detail in the literature using similar devices[6;20].

A quite surprising result came from changes observed in the lens thickness over time even when not subjected to environmental dehydration that could potentially accelerate the dehydration of a medium-high water content lens[21; 22] and the subsequent reduction of thickness. Considering that no exposure of the lens to air between measurements was ensured during the acquisition process and the patient only remained with both eyes open for 10 to 20 seconds before measurement, another possible explanation for the thinning of the CL could be related to the different physiological conditions of the ocular surface compared to the packaging solution of the lens (0.9% sodium chloride solution). The average value of the CL thickness measured is slightly higher than that reported for a -3.00 Dby the manufacturer. However, the result obtained in this study with the HROCT (429.88±3.27 microns) is very close to the value obtained with an automatic Redher Thickness Gauge (Redher Developments, CA), specifically designed to measure soft contact lenses in the hydrated state, obtained in our lab for the -6.00 D lenses (438±1.3 microns) used in the current experiment. Similar values were also obtained for the same CL measured with the same instrument reported in a previous study published recently[14].

When analyzing the response of the cornea and lenses across the sample, a quite consistent thinning effect of the lens was observed while the stromal thickening was quite variable among subjects, ranging from 20 to 40 microns in fitted eye and 5 to 10 microns in the control eye. This could be also anticipated considering the inter-individual variability of the edema response[23]. It is relevant to highlight that all corneas wearing the lenses and those that served as controls showed stromal edema. Closer agreement between the edema response after 90 minutes between lens-wearing eye and control eye agrees with the results reported by Fonn et al[17] evaluating the edematous response to high and low-Dk soft contact lenses. They showed a correlation between the edema response of the fitted eye and the control eye that they attributed to a sympathetic swelling effect. Although part of the edema response observed in our study for the control eye could be due to physiological swelling in closed eye conditions, the correlation found after 90 minutes between the edema responses of both eyes could also imply some sympathetic swelling effect. A closer inspection to the standard deviation values for the stromal response expressed as percentage shows an increase over time, which could be interpreted as a more uniform response to hypoxia in the short term while the longer response is more variable among individuals. The opposite is observed for epithelial changes showing a trend towards a decrease in the standard deviation values with time, which could be interpreted as a larger inter-individual dependency immediately after lens insertion with a trend towards uniformity over time.

Changes in the lens material (thickness and, likely, shape) should be further investigated under open eye conditions since it could help to understand the sometimes dramatic shifts in lens-to-cornea relationships while settling on the ocular surface. In clinical practice a period of 10 to 30 minutes is recommended before a final conclusion can be reached with regards to the CL fitting, but time required to achieve this equilibrium could be longer for thicker materials, however.

Since OCT is an optical-based method, changes in the refractive index of the media could adversely affect thickness measurements. For example, measurements taken while the lens is placed on the eye could adversely affect subsequent measurements of the corneal layers. In order to test this hypothesis, stromal and epithelial thickness were measured before (baseline) and immediately after lens insertion (t=0'). Considering that no significant changes were detected, it can be concluded that the method is as accurate for measuring corneal layer thicknesses with lens *in situ* as it is without the lens, since the observer is capable of detecting the boundaries of the different corneal layers and lens surfaces,. This was expected since the refractive index of the hydrophilic polymer of the lens is close to that assumed for the cornea, and important since several conditions such as therapeutic use of contact lenses would benefit from assessing the corneal response without lens removal.

However, when carrying out other experiments involving other types of lenses (i.e. PMMA materials or low-Dk RGP materials with refractive indices well above 1.4) this potential source of error should be considered. In a preliminary study conducted by the authors using the same instrument, the estimated thickness of a mini-scleral RGP lens made of medium-Dk material changed as much as 15 microns when compared with the value reported by the manufacturer, while the differences were negligible for soft and high-Dk RGP contact lenses. However, a statistical analysis to test the hypothesis of a potential influence of the refractive index on the OCT measurements could not be carried out in that study [14]. Furthermore, OCT might be sensitive to changes in corneal refractive index due to changes in corneal hydration after inducing edema[6]. However, potential errors induced in edema estimation must be below 3%[24], with some authors suggesting this could be as low as 0.02%[25].

In summary current OCT technology opens new and fascinating possibilities for evaluating tissue response as well as the behavior of materials used to compensate visual defects or as therapeutic tools. The methodology used in the present study can bring new insights into the corneal structure in several diseases (i.e. keratoconus and other ecstatic conditions,…), corneal changes in response to mechanical and physiological interactions (i.e. hypoxia, corneal reshaping, refractive surgery,…), measure corneal status under a therapeutic contact lens, among other.

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Involved in design of the study (JG-M, AC, JJ); conduct of the study (JG-M, AC, SCP-M); analysis and interpretation (JG-M, AC, SCP-M, DM-C, JJ); writing the article (JG-M, AC, SCP-M, DM-C, JJ, RM-M); critical revision (AQ, JG-M, JJ); final approval (AQ, CV-C, JG-M, JJ); data collection (JG-M, AC, SCP-M, SG-L, JJ, TF-B, RM-M); management of patients and equipments (JG-M, AC, SCP-M, DM-C, JJ, RM-M); statistical expertise (JG-M, AC, DM-C, JJ, RM-M) and literature review (JG-M, AC, SCP-M, DM-C).

The study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before all the interventions and they also gave their consent to treat their clinical data anonymously for research purposes.

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